

OBSERVATIONS ON BENZEDRINE

BY

ERICH GUTTMANN, M.D.,*Rockefeller Research Fellow*

AND

WILLIAM SARGANT, M.B., M.R.C.P.*(From the Psychiatric Research Unit, The Maudsley Hospital, London)*

Benzedrine was first introduced into therapeutics by Prinzmetal and Bloomberg (1935) for the treatment of narcolepsy. They found it more efficacious than ephedrine in bringing about symptomatic relief in this condition, and their claim has subsequently been confirmed. When they began their work little was known of the effects of the drug on man, though some physiological investigations had already been made on animals (Alles, 1933; Prinzmetal, 1933). In the same year Peoples and Guttmann made an independent study of its pharmacological actions at the Maudsley Hospital. Certain hitherto unrecorded psychological effects resulting from the administration of the drug to man were observed. In a preliminary report (Peoples and Guttmann, 1936) on these findings it was suggested that benzedrine might have therapeutic applications other than the treatment of narcolepsy. Numerous people have since experimented with the drug and a few have already indicated their findings, some workers confining their investigations to its use in depression, and others dealing with its wider psychophysiological actions (Guttmann, 1936; Myerson, 1936, 1937; Myerson and Ritvo, 1936; Nathanson, 1937; Solomon and Prinzmetal, 1937); one paper has specially stressed possible dangers and contraindications (Anderson and Scott, 1936).

It is the purpose of this paper to report further personal observations of an experimental and therapeutic nature which have been collected since the preliminary communication on this subject (Peoples and Guttmann, 1936). Benzedrine has now been given to over 250 in-patients, out-patients, and normal subjects at this hospital; in a proportion of these only the subjective and objective results of administration have been noted, but in more than a hundred cases systematic experiments were carried out.

Benzedrine (β -phenylisopropylamine) is an adrenaline-like drug with an action on the vegetative nervous system. It paralyses intestinal activity, raises the blood pressure, and produces other vasomotor effects to be described in detail later. It is also used in the form of an inhalant to bring about constriction of the nasal mucous membrane. It interferes with sleep and may cause pronounced psychological changes. Blood-sugar levels are not affected (Peoples and Guttmann, 1936), and work done at the Central Pathological Laboratory of the L.C.C. Mental Service under Dr. Golla indicates that it does not produce any significant alteration in the basal metabolic rate or impedance angle. An inhibiting action on the sphincters of the bladder and rectum and an increase in the number of circulating red cells have also been recorded after its administration (Myerson, 1937; Myerson and Ritvo, 1936; Nathanson, 1937).

Our own investigations have been mostly confined to the action of benzedrine on the cardiovascular system and the psychological changes observed. Small doses were generally employed, ranging from 10 to 30 mg., larger

amounts only being used under strict supervision for experimental purposes. It was given by the mouth in the form of tablets.

Blood Pressure and Other Cardiovascular Effects

The influence of small doses on the blood pressure is limited. Fluctuations of 10 to 30 mm., however, were sometimes observed. This degree of alteration falls within the limits of experimental error and normal physiological variation, but it was attributed to benzedrine when it was repeatedly observed in the same patient under exactly similar experimental conditions. Furthermore, the degree to which the blood pressure altered with the standard dose seemed almost constant for any individual. As a general rule benzedrine was given only to those who showed no cardiovascular disease; but a few cases who had extrasystoles, apparently of a functional type, were included in our experiments. We witnessed none of the severer complications reported by Anderson and Scott, but the more vasolabile subjects sometimes complained of dizziness, shivering feelings, palpitations, tremor, or anorexia. These symptoms were more frequent during the first hour after taking the drug, coinciding with the time taken for its full effect to develop. The speed of absorption seems to influence the occurrence of these reactions, so that it is inadvisable to give the tablets on an empty stomach. Other autonomic disturbances rather than the actual rise in blood pressure appeared mainly responsible for these symptoms, and sometimes they were precipitated or increased by physical effort and emotional upset.

Psychological Effects

Benzedrine produces a general psychological stimulation. Subjectively this is experienced as increased confidence, initiative, and ease in making decisions, sometimes combined with a feeling of restlessness. There is also a pronounced impulse to talk more than usual. The restlessness may be pleasant or unpleasant, depending on the degree to which it is accompanied by the somatic symptoms described above; in the absence of these a pleasant sensation is reported which often amounts to a real degree of euphoria. Objectively, it is the increased talkativeness and activity which most impress the outside observer. Thinking processes appear to be speeded up without impairing attention, concentration, or judgement, and the features of total personality make-up that seem to benefit most are retardation, indecision, mild depression, and hesitation. It has already been shown that in certain cases intelligence test scores are improved (Sargent and Blackburn, 1936). Medical colleagues and others who have themselves taken benzedrine have found it of definite value in such tasks as lecturing or taking an examination. It also helps to remove mental fatigue brought on by excessive work or worry. Important interviews of various kinds have been tackled more confidently than usual under benzedrine, especially those requiring quick thought and ability to talk convincingly and fluently.

When the dose is sufficient to cause physical or psychological changes, disturbances of sleep are rarely absent. There is difficulty in getting to sleep, and sometimes patients wake up during the night or too early in the morning. This sleeplessness is not always unpleasant. It is reported by some as "lying contentedly in bed," in contrast with the distressing restlessness of the insomnia in many nervous illnesses. The effects of the drug often persist the following morning, so that the subject gets up

feeling surprisingly fresh and active in spite of the comparative lack of sleep. No changes in the blood pressure have been found to remain the following day.

Normal Subjects.—In different subjects there is a wide variation in the response to benzedrine. It has been found almost impossible to correlate exactly an individual's response to the drug with his personality make-up. This can only accurately be determined by trial. However, as a general rule it may be said that in the doses used benzedrine tends to exaggerate some of the innate characteristics of the personality besides producing the effects described above. For instance, one can assume that some of Anderson and Scott's subjects who complained of "a funny feeling not quite amounting to pain" seven hours after taking benzedrine must be somewhat hypochondriacal, as, indeed, was expressly stated in one of their case reports. We ourselves are diffident of giving the drug to people who have hypochondriacal tendencies. Mildly obsessional personalities may also be upset by it, but in this group there were some who responded extraordinarily well, especially hesitant individuals who show a tendency to obsessional doubt and difficulty in making up their minds about any small or unimportant matter. Persons with cyclothymic tendencies had by far the most constant and beneficial reaction from the drug, and it usually gave them a characteristic euphoria.

Depressive Illnesses.—Mild depression accompanied by retardation is the most favourable of all psychological disorders for benzedrine therapy. It has been found that these patients may be carried over periods of temporary disability by regular medication. In several cases the possibility of benefit being due to suggestion was ruled out by the occasional substitution of "inert" tablets which never produced the same effects. Severe depressions and depressive stupor do not react to the drug in the same way; small doses have little effect and heroic doses appear to produce anxiety symptoms. Other workers, in personal communications to us, have reported "dramatic" effects with 40-mg. doses in severe depressions, but it has been our experience that such improvement is transient and resists repeated medication. At the end of a depression, however, its use is more promising. It may enable a patient to start work or take the initial steps to social readjustment earlier than without it.

At the beginning of an endogenous depression it may also be of use by delaying for a time the onset of the more severe stages of the illness. For instance, it enabled one patient who felt he was developing one of his recurrent depressive attacks to carry on important work for an extra week and to make business arrangements for the period of his approaching illness. By the next week, however, the endogenous retardation was too severe to yield to the drug. It is interesting to note that Krapf (1936) observed a marked variability of the blood pressure at the beginning and end of endogenous depressions, while during the main period of the illness the blood pressure is relatively stable. Thus the periods in which benzedrine is most efficient appear to coincide with times at which the blood pressure is most variable.

Anxiety States.—Anxiety is common in many psychiatric syndromes, and when the somatic symptoms of anxiety, such as palpitation, tremor, etc., are prominent, benzedrine is usually contraindicated, as these symptoms are often exaggerated by the drug. A few patients, however, reported that they did not worry so much about anxiety symptoms when taking benzedrine, and some cases clinically labelled as anxiety neurosis considerably improved. This finding is probably due to the beneficial

effect of benzedrine on symptoms of indecision or depression complicating the picture.

Schizophrenic Illness.—Because of the variety of clinical manifestations met with in schizophrenia it is difficult to make any general statement as to the effect of the drug. Nevertheless, certain patients may benefit—namely, those in whom there is a lack of initiative. These welcome the stimulation produced by benzedrine, and objective improvement in their activity also occurs. One of our patients, an artist who had given up drawing during his illness, started again when given benzedrine; but he only drew on his benzedrine days and not on the control days. Another patient convalescing from a schizophrenic illness reported a similar relief from his persistent feeling of fatigue and resumed playing the piano. It was impossible, however, to interrupt a schizophrenic stupor with the drug, and it definitely made some hallucinated and deluded patients worse. We found it particularly dangerous to give benzedrine to those in whom a superficial depression masked the underlying schizophrenic illness. It caused a severe exacerbation in the symptoms of one such patient, who would almost certainly have attempted suicide while under its influence had she not been subject to hospital supervision.

Narcolepsy.—The claims of Prinzmetal and Bloomberg, (1935) have been confirmed by our observation and those of others. One patient with idiopathic narcolepsy has taken 10 to 20 mg. a day for over a year with constant relief from her symptoms, which for many years had resisted other forms of treatment. We observed a similar effect in a patient in whom the narcoleptic attack appeared symptomatic of cerebral arteriosclerosis, and the narcoleptic attacks in the post-encephalitic syndrome are also lessened by the drug.

Relation of Psychological Effects and Blood-pressure Alterations

Experimental observations on individual cases have shown that the rise in blood pressure and the psychological phenomena observed do not necessarily coincide in any individual. Patients with little alteration in blood pressure may exhibit profound psychological stimulation, and vice versa. This experimental finding in individual cases was borne out by recording the blood pressures of forty-eight subjects during intelligence tests under benzedrine. Ten of them increased their test scores by ten points or more, but it was found that only one of these showed a concomitant rise in blood pressure of over 20 mm. The cases with rises of 20 mm. or more, with this one exception, failed to attain the same degree of improvement in their test scores. We also saw a paradoxical fall in the blood pressure after giving 10 mg. of benzedrine to certain cases of anxious depression. We assume that in these cases the psychological effect of the drug was sufficient to influence the emotional tension (with its accompanying increase of blood pressure), while the dose was too small to have a physiological effect on the blood pressure itself.

Practical Considerations

We have found that benzedrine gives the best results when used in doses of 10 to 30 mg. Larger amounts often produce so much palpitation, tremor, and rise in blood pressure that the concomitant psychological effects are apt to be destroyed. The smallest dose that will bring about the required psychological stimulation should always be used, and this is determined by starting with a dose of 10 mg. and then increasing it if necessary. The drug

should be given before midday if sleeplessness is to be avoided; on the average the effect tends to remain at a maximum for about five hours and takes an hour or more to develop fully. The psychological stimulation is not always maintained on continuous daily administration. Some patients complain that it loses its euphorizing effect after a few days, while the disagreeable features become more predominant.

The possibility of addiction needs to be guarded against, and the case of a person who had been purchasing benzedrine at chemists' shops without medical supervision has already come to our notice, though none of our own patients have so far shown a tendency to addiction. The preponderance of disquieting somatic symptoms over the feeling of euphoria when large doses are taken, and the sleeplessness, make us think that addiction will be rare. At present, however, benzedrine may be purchased at any chemist's shop without prescription, and this seems inadvisable with a drug all the properties of which have yet to be fully investigated. It must also be emphasized that the therapeutic indications for its use apart from the treatment of narcolepsy have not been exactly formulated. It is to be hoped that this drug will not be discredited by misuse.

We wish to thank Professor E. Mapother for his kind permission to use the clinical material of the Maudsley Hospital and Dr. F. Pilkington for help in the preparation of this paper.

REFERENCES

- Alles, G. (1933). *J. Pharmacol. exp. Therap.*, **47**, 339.
 — and Prinzmetal, M. (1933). *Ibid.*, **48**, 161.
 Anderson, E. W., and Scott, W. C. M. (1936). *Lancet*, **2**, 1461.
 Guttmann, E. (1936). *J. ment. Sci.*, **82**, 618.
 — (1936). *Proc. roy. Soc. Med.*, **29**, 1387.
 Krapf, E. (1936). *Die Seelenstörungen der Blutdruckkranken*, Leipzig and Vienna.
 Myerson, A. (1936). *Arch. Neurol. Psychiat.*, Chicago, **36**, 816.
 — (1937). *J. Neurol. ment. Dis.*, **85**, 202.
 — and Ritvo, M. (1936). *J. Amer. med. Ass.*, **107**, 24.
 Nathanson, M. H. (1937). *Ibid.*, **108**, 528.
 Peoples, S. A., and Guttmann, E. (1936). *Lancet*, **1**, 1107.
 Prinzmetal, M., and Bloomberg, W. (1935). *J. Amer. med. Ass.*, **105**, 2051.
 Sargant, W., and Blackburn, J. M. (1936). *Lancet*, **2**, 1385.
 Solomon, Ph., and Prinzmetal, M. (1937). *J. nerv. ment. Dis.*, **85**, 202.

M. Dechaume (*Presse méd.*, March 24, 1937, p. 451) reports a case in which intense pain followed the removal of a wisdom tooth from the lower jaw on the left side. Extraction was carried out under local anaesthesia, and during the process severe pain radiating to the ear was felt, and the operation could not be completed until the nerve trunk had been injected. A small filament resembling a nerve came out of the socket, and this was cut off, slight pain being felt in the chin during the process. This was followed by intolerable pain in the left half of the face. Three days later an injection of novocain, without adrenaline, was given around the facial artery so as to paralyse the sympathetic nerves, and this relieved the pain. The following day severe pain recurred, but became less intense after a second injection. On examination the socket was found to contain pus, and as an antiseptic could not be used on account of the pain a plug of gauze soaked in novocain was applied for several seconds. During the next week symptoms subsided, with the exception of anaesthesia in the left half of the lower lip and chin. It is pointed out that, although it was unusual that a nerve should have been torn during the removal of the wisdom tooth, this could not have been foreseen. Injection of the sympathetic for relief of pain has been tried successfully in other instances. The injection causes a vasodilatation and increases the blood supply to the part, but the effect is transitory and the treatment must be repeated.

TECHNIQUE IN OPERATIONS ON THE KNEE-JOINT*

BY

ERIC I. LLOYD, M.B., B.Ch., F.R.C.S.

Orthopaedic Surgeon to the Royal Northern Hospital;
 Surgeon to the Hospital for Sick Children, Great Ormond Street

The knee-joint has been derived from the fusion of three articulations, and this makes it the most complex as well as the largest joint in the body. It is only comparatively recently that this field has been made safe for surgery, and the layman still has a fear that the removal of a semilunar cartilage may leave him with a stiff knee. Such an event is now a rare calamity, but it has occurred and still occasionally does so. Knee-joint surgery is recognized to demand the most careful technique, and I am going to describe a scrupulously careful procedure which stops short of fussiness. At the same time we shall have an opportunity of seeing that technique in these cases must include the care of a patient both before and after the operation.

The chief bogey is sepsis, and it can only arise in one of two ways—namely, by infection from without—that is, errors in aseptic technique—and by infection from within—that is, from a focus of infection elsewhere in the body. We must note that either of these events is greatly facilitated by the presence of blood in the joint. Blood is an excellent culture medium for organisms, and both a haematoma and a haemarthrosis are readily infected from without or from within. We all know that a haematoma in an operation wound prolongs convalescence for only a few days if it is at once evacuated, but becomes a much more serious trouble if it lies hidden until infection has occurred. A haemarthrosis differs from a haematoma only in its size and the character of its limiting membrane. A dry joint is probably quite able to cope with occasional organisms, which rapidly, however, become a massive infection when incubated at body temperature in a large blood-filled synovial cavity.

Preliminary Examination

Preliminary examination of all patients with cartilage injuries should include examination of the teeth. It is certainly dangerous to open a knee-joint while dental sepsis remains untreated. If any extractions or fillings are necessary it is wise to allow at least three weeks to elapse before opening the knee-joint. Equally, any other infection, such as tonsillitis, boils, or an infected antrum, demands postponement of the operation until the potential danger has been removed.

Preparatory Dressings

The skin is one of the chief dangers: the preparatory dressing is an important prelude to the operation, and a couple of days is not too long to devote to it. No procedure can make the skin completely sterile because antiseptics can only act superficially. We must do the best we can and then proceed on the assumption that we have only been partly successful. The whole limb from the toes to the groin is first shaved and then washed with soap and water. Methylated spirit compresses are applied to this area for twenty-four hours, and a solution of iodine in spirit is next painted on the skin. The whole limb is then covered with sterile towels, which are

* Based on a lecture delivered at the Hospital for Sick Children, Great Ormond Street.